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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,101	11/03/2006	Norio Teramae	3716638-00002	4072

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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
01/27/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chicago.patents@klgates.com

Office Action Summary	Application No.	Applicant(s)	
	10/599,101	TERAMAE ET AL.	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-26* is/are pending in the application.

4a) Of the above claim(s) *21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/26/2010 has been entered. Claims 12-26 are pending. Claims 21-26 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 12, 13, 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bao et al (20030129611, July 2003) in view of Yoshimoto et al. (Chemical Communication, Issue 24, pages 2960-2961, October 2003). Regarding claim 12, Bao et al teach a method for detecting a gene mutation comprising: forming a gap part at a position opposed to a target based by forming a double stranded nucleic acid from a single stranded nucleic acid having a target based composed of one or more continuous bases and two partial sequences thereof with the target base there between, and two single stranded detecting nucleic acids complementary to the two partial sequences of bases, wherein the single-stranded detecting nucleic acid form the gap part to the position of the target based on the single stranded target nucleic acid and identifying the gene mutation using fluorescent detection that uses resonance energy transfer (see Figures 1 and 2; wherein SEQ ID NOS: 11 and SEQ ID NO: 12 represent the two single stranded nucleic acid complementary to the two partial sequences with the target base and SEQ ID NO: 10 representing the target sequence having a mutation between SEQ ID NOS: 11 and 12).

Bao et al differs from the instant invention in that the reference does not teach wherein a hydrogen bond is formed by the target base and a receptor by inserting a receptor having hydrogen bonding characteristics into the double stranded nucleic acid and then identifying the gene mutation where the receptor bonds to the target base.

Yoshimoto et al provides a method similar to that of Bao et al for fluorescence detecting of a mutation in a target nucleic acid by hydrogen bond forming small compounds (see Figure 1 and col. 1-2 of page 2960). Yoshimoto et al teach wherein the method comprises forming a double strand nucleic acid from a single stranded nucleic acid having a target base composed of one or more continuous bases and two partial sequences there with the target base there between; and a probe comprising two separate regions, wherein each region is complementary to each of partial sequences with the target base there between and identifying the gene mutation, wherein said identifying step comprising forming a hydrogen bond by the target base and a receptor by inserting a receptor having hydrogen bonding characteristics into the double stranded nucleic acid (see Figure 1 and col. 1-2 of page 2960). Yoshimoto et al recognizes that while such method as high density arrays, primer extension methods, real-time PCR, and Invader assays (which includes various forms of fluorescent detections), all are used for detecting a mutation in a target nucleic acid, these methods require several time consuming steps, use of several kinds of fluorophore-labeled oligonucleotides (ODNs) and/or special enzymes. (see first paragraph of page 2960 at col. 1). Yoshimoto further recognizes that while mass spectroscopy has recently been applied to genotyping, it's use is at a disadvantage because careful treatment are required to ensure purity of the sample. Yoshimoto attempt to solve the problems of those techniques noted above and taught by Bao et al by providing a quick, simple and cost effective method for the routine detecting of mutations (see col. 1 of page 2960 for discussion).Yoshimoto et al teach that they expect that the use of low molecular weight

ligands as recited in their method offers a novel approach to a simple, low cost assay for SNP (mutation) typing (see page 2961, col. 2, lines 10-14).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to have been motivated to modify the method of Bao et al to encompass the use of a receptor having hydrogen bonding characteristics to detect the gene mutation in the target nucleic acid rather than the donor and acceptor molecular beacons which result in FRET as taught by Bao et al to alleviate some of the disadvantage of the FRET system and improve gene mutation detection. The ordinary artisan would have been motivated to use the receptor having hydrogen bonding characteristics based on the advantages taught by Bao et al that such method provides a more simple, quick and cost-effective approach to mutation typing. Likewise, it would have been *prima facie* obvious to the ordinary artisan at the time of the claimed invention that one could substitute one known option for another in assays for mutation typing, namely the use of receptor having hydrogen bonding characteristic rather than dual molecular beacons using FRET as taught by Bao et al or any of the other assays recited above, since all of these techniques are within the ordinary artisan's technical grasp and further since the use of a receptor having hydrogen bonding characteristics, such as those recited in the claims, do not negatively alter, affect or modify fluorescent detection of the target mutation. Thus, one of ordinary skill in the art at the time of the claimed invention could expect a reasonable expectation of success and attempt to improve detection of the target mutation based on the combined teachings of Bao et al in view of Yoshimoto et al.

Regarding claim 13, Yoshimoto et al. teach wherein the receptor has a heterocyclic aromatic group and is stabilized by the formation of a hydrogen bond to the target base and a stacking interaction with the base adjacent to the receptor to form a pair with the target base (see Table 1 on page 8982 where structure of AMND = receptor of instant claim is shown. The structure of AMND shown has a heterocyclic aromatic group. See page 8982 col. 2 par. 1 where determination of stability between AMND and C indicates the significant role of stacking of AMND with nucleobases flanking the AP site is taught. Also see last line of this par. where conclusion is stated. "Therefore, AMND should bind to C in cooperative fashion, that is, hydrogen bonding with C and stacking with nucleobases flanking the AP site". Thus Yoshimoto et al. teach wherein the receptor has a heterocyclic aromatic group and is stabilized by the formation of a hydrogen bond to the target base and a stacking interaction with the base adjacent to the receptor to form a pair with the target base).

Regarding claim 14, Yoshimoto et al. teach wherein the receptor is at least one of a naphthylidine derivative, a quinoline derivative, a pteridine derivative, a coumarin derivative, an indazol derivative, an alloxazine derivative and amyloride (see page 8982 par. 2 where AMND taught is a methyl napthyridine hence teaching wherein the receptor is a naphthylidine derivative).

Regarding claim 18, Yoshimoto et al. teach wherein the receptor shows fluorescence emitting characteristics and the gene mutation is identified as a change of fluorescence strength of the double-stranded nucleic acid into which the receptor is inserted (see fig. 4 where the receptor shows fluorescence emitting characteristics and

the gene mutation is identified as a change of fluorescence strength of the double-stranded nucleic acid into which the receptor is inserted).

5. Claims 15-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bao et al in view of Yoshimoto et al. as applied to claim 12-14 and 18 above, and further in view of Nakatani et al. (2001) J. Am. Chem. Soc. 123: 12650-12657 (provided by Applicant in IDS).

Regarding claim 15, Boa et al in view of Yoshimoto et al. teach detection of a gene mutation comprising forming a gap part at a position opposed to a target base by forming a double stranded nucleic acid as previously described above.

Bao et al and Yoshimoto et al. do not expressly teach wherein the receptor is fixed to a substrate. However the use of solid supports in methods of detecting mutations by the techniques mention previously are well-known in the prior art.

For example, Nakatani et al. teach wherein the receptor is fixed to a substrate (see page 12651 col. 2 par. 2 where naphtyridine derivative referred as compound 2 is immobilized onto dextran coated gold surface to develop a mismatch detecting sensor useful for a surface Plasmon resonance (SPR) assay.

Regarding claim 16, Nakatani et al. teach wherein the gene mutation is identified on the basis of the change of a signal strength of a surface plasmon resonance due to the bond of the target base and the receptor (see page 12651 col. 2 par. 2 where a mismatch detecting sensor useful for a surface plasmon resonance (SPR) assay is described. They go on to teach differentiation of 652 bp of PCR products of a G/C

heterozygote from those of a G/G homozygote of HSP70-2 gene regarding the base at a nucleotide number 2345. Thus teaching Nakatani et al. teach wherein the gene mutation is identified on the basis of the change in signal strength of a surface plasmon resonance due to the bond of the target base and the receptor).

Regarding claim 17, Nakatani et al. teach development of sensor where a component of the reaction mix namely receptor is fixed on substrate to develop sensor that is suitable for surface plasmon resonance (SPR) assay.

In the instant claims (15 and 17) applicant recites fixing a different component of the assay namely one detecting nucleic acid to a substrate instead of the fixing the receptor as taught by Nakatani et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Nakatani et al. in the method of Bao et al and Yoshimoto et al. to fix any of the components either the receptor or the one detecting nucleic acid to a substrate to form the sensor and then add the remaining components required to form the double stranded hybrid (claims 15 and 17). Thus, Nakatani et al. teach wherein one detecting nucleic acid is fixed to a substrate and the double-stranded nucleic acid is formed by dropping on the substrate the single-stranded target nucleic acid, the other detecting nucleic acid and the receptor.

See 2144.04 Legal Precedent as Source of Supporting Rationale [R-6] - 2100 Patentability IV. CHANGES IN SIZE, SHAPE, OR SEQUENCE OF ADDING INGREDIENTS C. Changes in Sequence of Adding Ingredients. See *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process

steps is *prima facie* obvious in the absence of new or unexpected results); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is *prima facie* obvious.).

Regarding claims 19 and 20, Yoshimoto et al. teach wherein the receptor shows fluorescence emitting characteristics and the gene mutation is identified as a change of fluorescence strength of the double-stranded nucleic acid into which the receptor is inserted (see Fig. 4 where the receptor shows fluorescence emitting characteristics and the gene mutation is identified as a change of fluorescence strength of the double-stranded nucleic acid into which the receptor is inserted).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Nakatani et al. in the method of Bao et al in view of Yoshimoto et al. The motivation to do so is provided to one of ordinary skill in the art by the teachings of Nakatani et al that “We have developed a mismatch-detecting sensor useful for a surface Plasmon resonance (SPR) assay by immobilizing 2 (note added by Examiner 2 = naphthyridine compound) onto the dextran-coated gold surface." (see page 12651 col. 2 par. 2). They go on to teach its successful use in determining gene mutation. Hence, one of ordinary skill in the art at the time of the claimed invention would have a reasonable expectation of success in being able to develop a sensor for detecting mutations using the receptor taught by Yoshimoto et al. in the method of Boa et al and immobilizing the components to a surface as taught by Nakatani et al for the obvious benefit of caring out additional and more sensitive and

specific means of detecting the mutation, said means being surface plasmon resonance.

Response to Arguments

6. Applicant traverses the rejections on the following grounds: Applicant summarizes the Examiner's Rejections and case law concerning KSR and states that Boa et al do not teach detection of mutation located in a gap part formed by two single stranded detecting nucleic acids. Applicant states that Bao et al does not provide for the formation of a gap part in between both the donor and acceptor beacons at a position opposed to a target base. Applicant states that Yoshimoto does not remedy the deficiency of Bao and therefore they cannot obviate the instant claims. Applicant states that the references are not combinable and further does not teach the advantages noted in the instant invention.

7. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: Contrary to Applicant arguments, the prior art of Bao et al clearly show a target sequence comprising a mutation and two probe sequences which hybridize on both sides of the target comprising the mutation such that a gap is formed between the two probes opposed of the target (figures 1 and 2 and Examples which teaches using the probes to detect a K-ras codon mutation. While the Examiner agrees that the reference of Bao et al focuses on molecular beacons and fluorescent detection, the Examiner notes that the secondary teachings of Yoshimoto provides the missing element not found in Bao et al and provides sufficient motivation for combining the teachings for detection of a specific target mutation.

Additionally Applicant is reminded that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 2007) (citing *KSR,* 82 USPQ2d at 1396). Thus, Applicant's arguments are not found persuasive as the gap limitation as argued by Applicant is expressly taught in both the teachings of Boa et al as shown in the Figures 1 and 2 and depicted in Yoshimoto et al as shown in the Figure 1.

In response to Applicant's arguments that the references are not combinable, Applicant provides no sufficient evidence to support the conclusion that the combination of Bao et al in view of Yoshimoto does not meet the limitations of the claims. MPEP states the arguments of counsel cannot take the place of evidence in the record. *In re Schulze,* 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant (see MPEP 716.01 (b). Further, Applicant is reminded that the Courts have established that "[A]n "obviousness finding was appropriate where the prior art 'contained *detailed enabling methodology* for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.'" *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988).

The court commented that "[r]esponding to concerns about uncertainty in the prior art influencing the purported success of the claimed combination, this court [in *O'Farrell*] stated: '[o]bviousness does not require absolute predictability of success ... *all that is required is a reasonable expectation of success*.'" Kubin, 561 F.3d at 1360 (citing In re O'Farrell, 853 F.2d at 903-904). It is the Examiner's position that the cited prior art provides sufficient evidence that one could expect a reasonable expectation of success in obtaining the claims invention using the combination of Boa et al in view of Yoshimoto as discussed in the prior Office action.

In response to Applicant's arguments concerning the advantages of the instant invention over the cited prior art, this argument is not persuasive, because the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In this case, this is especially true as neither the claims nor specification provides any evidence of unexpected results based on ease of detecting gene mutation and realization of low cost as argued by Applicant. MPEP states that "objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699,

705, 222 USPQ 191, 196 (Fed. Cir. 1984). Applicant's arguments are not found persuasive to overcome the prior art rejection(s).

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Conclusion

7. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/

Examiner, Art Unit 1637